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| PRE-APPEAL BRIEF REQUEST FOR REVIEW | Docket Number (Optional) 0020-4802P |
|---|---|

| | Application Number | Filed |
|---|---|---|
| | 09/743,750-Conf. #7730 | January 16, 2001 |
| | First Named Inventor: Ichiro AZUMA et al. | |
| | Art Unit: 1645 | Examiner: V. L. Ford |

Applicant requests review of the outstanding rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

[ ] applicant /inventor.

[ ] assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

[x] attorney or agent of record.
Registration number 36,623

[ ] attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/mjn/
Signature

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May 18, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[ ] *Total of 1 forms are submitted.

Docket No.: 0020-4802P
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ichiro AZUMA et al.

Application No.: 09/743,750 Confirmation No.: 7730

Filed: January 16, 2001 Art Unit: 1645

For: FORMULATIONS USEFUL FOR IMMUNOTHERAPY FOR CANCERS CONTAINING BACTERIAL COMPONENT AS AN ACTIVE INGREDIENT

Examiner: V. L. Ford

## PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed January 18, 2007, the appellant respectfully requests a Pre-appeal Brief Conference. This request is being filed concurrently with a Notice of Appeal.

### [II] Remarks

Applicants request withdrawal of the rejections of record as being clearly erroneous in fact and in law for the reasons set forth below.

### [III] Status of Claims

Claims 1-3, 5-8, 10-11 and 13-26 are pending in the present application. Claims 1-3, 5-8, 10-11 and 13-20 have been withdrawn by the Examiner. Claims 21-26 stand rejected.

### [IIII] Grounds Of Rejection To Be Reviewed

1) Rejection of claims 21-26 under 35 U.S.C. §102(b) as being anticipated by Yamamura et al. (U.S. 4,543,253) (hereinafter "Rejection (1)").

2) Rejection of claims 21-26 under 35 U.S.C. §102(b) as being anticipated by Yarkoni et al. (*Infection and Immunity*, 28(3): 881-886 (1980)) (hereinafter "Rejection (2)").

3) Rejection of claims 21-26 under 35 U.S.C. §102(b) as being anticipated by Zbar et al. (Journal of National Cancer Institute, V. 48, No. 3, pp. 831-835) (hereinafter "Rejection (3)").

4) Rejection of claims 21-26 under 35 U.S.C. § 112, second paragraph (hereinafter "Rejection (4)").

**Rejections 1-3 based on anticipation**

The instant invention is drawn to an oil-in-water emulsion wherein the emulsion is dispersed without crude particles, is negative for agglutination reaction with lectin, a *Bacillus Calmette-Guerin* cell wall skeleton is encapsulated in an oil, and the particle diameter of oil droplets is 100 μm or less. Applicants maintain the position that the Examiner has failed to establish a *prima facie* case of anticipation as required by U.S.C. § 102 for at least the following reasons:

1) The cited references fail to teach a product exhibiting the distinctive structural, physical and functional characteristics of the claimed product; and
2) The Examiner has failed to establish that the distinctive structural, physical and functional characteristics of the claimed product are inherently present in the cited references.

The Examiner notes that Yamamura et al. teaches compositions comprising a *Nocardia ruba* cell wall skeleton, squalene, a suspending agent and a dispersing agent. The Examiner asserts that certain claim limitations (i.e., emulsion negative for agglutination reaction with lectin, particle diameter of "25 μm" or "100 μm or less", homogeneous dispersion) would be inherent in the teachings of this reference. The Examiner contends that process limitations have not been given patentable weight, because the product claimed and the product of the cited reference appear to possess the same functional characteristics.

As to Yarkoni et al., the Examiner asserts that Yarkoni et al. teaches oil-in-water emulsions comprising *Mycobacterium bovis* BCG cell walls, squalene and Tween. The Examiner further asserts that certain claim limitations (i.e., emulsion negative for agglutination

reaction with lectin, particle diameter of "25 μm" or "100 μm or less", homogeneous dispersion) would be inherent in the teachings of this reference. The Examiner contends that process limitations have not been given patentable weight, because the product claimed and the product of the cited reference appear to possess the same functional characteristics.

As to Zbar et al., the Examiner asserts that Zbar et al. teaches a composition comprising BCG cell walls and mineral oil droplets having a diameter of less than 1 μm to greater than 15 μm. The Examiner further asserts that certain claim limitations (i.e., emulsion negative for agglutination reaction with lectin) would be inherent in the teachings of this reference. The Examiner has not given weight to any process limitations.

Yamamura et al. is directed to a storable pharmaceutical composition comprising a dehydrated solid mixture of microbial cell wall skeleton, a vehicle oil and suspending and dispersing agents. Yamamura et al. describes compositions comprising *Nocardia rubra* cell wall skeleton, rather than *Bacillus Calmette-Guerin* cell wall skeleton, as presently claimed. Yamamura et al. does not teach use of an organic solvent during preparation of the emulsion.

Yarkoni et al. is directed to emulsified *Mycobacterium bovis* BCG cell walls and examines the influence of oil types and surfactant concentrations on the efficacy of emulsions. Yarkoni et al. does not teach the use of an organic solvent during the preparation of the emulsion.

Zbar et al. is directed to tumor suppression by cell walls of *Mycobacterium bovis*. Zbar et al. does not teach the use of an organic solvent during the preparation of their emulsion.

Upon careful review of the cited references, it is clear that the references do not teach each and every limitation of the instant invention. At least the following physical characteristics are absent from the emulsions disclosed by the references: 1) an oil-in-water emulsion lacking crude particles 2) negative for agglutination reaction with lectin, 3) comprising a *Bacillus Calmette-Guerin* cell wall skeleton encapsulated in an oil 4) with an oil droplet particle diameter of 100 μm or less. As explained above, the processes used to create the emulsions of the prior art **all** ***lack a step wherein an organic solvent is added to the cell wall skeleton and the oil prior to addition of the aqueous phase to the emulsion.***

The oil-in-water emulsion according to the present invention is characterized in that the emulsion has the following properties: 1) lacks any "crude" particles; 2) is negative for agglutination reaction with lectin; 3) a BCG-CWS is encapsulated in an oil to form oil droplets; and 4) the particle diameter of the oil droplets is 100 μm or less.

These properties are provided in emulsions by means of the process defined in the presently pending claims, steps (a), (b) and (c), and especially by the use of an organic solvent in the step of dispersing the BCG-CWS component in oil.

First, the Examiner has **failed** to establish that the distinctive physical, structural and functional characteristics of the inventive product are inherently present in the products of Yamamura, Yarkoni and Zbar. That a certain result or characteristic *may* occur or be present in the prior art is **not** sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is **necessarily** present in the thing described in the reference". *In re Robertson*, 169 F.3d 743, 49 USPQ2d 1949 (Fed. Cir. 1999).

In the present instance, the emulsions of the invention are made by a process distinct from the process used to make the emulsions described by the cited references. Therefore, there is simply no basis whatsoever for the Examiner to take a position that the resulting emulsions of the invention and of the prior art are the same. The Examiner has made a clear error of fact and law and the instant rejections over Yamamura, Yarkoni and Zbar should be reversed.

Furthermore, in presenting the rejections, the Examiner expressly indicates that a showing of a difference in some physical property of the emulsions, "such as ... greater stability ..." can serve as a basis for patentable distinction between the claimed product and the prior art. As evidenced by the Declarations of Dr. Nomura and Dr. Koseki (of record), failure to include an organic solvent during dispersion of the CWS component in oil results in the appearance of some very large particles in the resulting emulsion (that is, the particle size is not uniform and includes some "crude particles") and lower emulsion stability. Thus, there is ample evidence of record in the present instance that is of just the sort of showing the Examiner admits is sufficient to distinguish the invention from the prior art.

As to Yamamura, the Koseki Declaration shows that the paste of BCG-CWS and an oil, which is the starting material for emulsification, obtained according to the method of Yamamura et al. is not suitable for preparing a good emulsion. In particular, the paste resulting from the oiling steps of Yamamura et al. do not adequately coat the powdered CWS material and so fail to provide a sufficient dispersion. The preparations manufactured in accordance with the teachings of Yamamura et al. do not provide uniform emulsions. Rather, large amounts of the BCG-CWS material remain un-emulsified and form "crude particles". Failure to include and organic solvent at the step of dispersing the BCG-CWS material in Yarkoni and Zbar provides a similar result of lack of complete emulsion and formation of "crude particles" and lower emulsion stability. Thus, as evidenced by the Declarations of record, the products of Yamamura, Yarkoni and Zbar do not exhibit the same characteristics as the product of the present invention.

Plainly, the references fail to explicitly or inherently teach each and every limitation of the present invention. Furthermore, there is substantial evidence of physical differences between the emulsions of the invention and those of the prior art. Thus, rejections (1), (2) and (3) amount to ***clear error*** on the Examiner's part. Accordingly, withdrawal of Rejections (1), (2) and (3) is respectfully requested.

**Rejection (4) based on 35 U.S.C. § 112, second paragraph**

The Examiner rejects claims 21-26 due to her inability to understand what is meant by "crude particles." The Applicant has noted that the specification, at page 18, in the second paragraph, plainly defines a crude particle as one that is visible and has a diameter of 100 μm or more. Thus, the Examiner's reasons for presenting this rejection are not understood and the rejection should be withdrawn.

Dated: May 18, 2007

Respectfully submitted,
By _____
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